

Delayed Anaphylaxis to Red Meat Masquerading as Idiopathic Anaphylaxis

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Anaphylaxis is traditionally recognized as a rapidly developing combination of symptoms that often includes hives and hypotension or respiratory symptoms. Furthermore, when a specific cause is identified, exposure to this cause is usually noted to have occurred within minutes to 2 hours before the onset of symptoms. This case is of a 79-year-old woman who developed a severe episode of anaphylaxis 3 hours after eating pork. Before 2012, she had not experienced any symptoms after ingestion of meat products. Delayed anaphylaxis to mammalian meat has many contrasting features to immediate food-induced anaphylaxis. The relevant IgE antibody is specific for the oligosaccharide galactose- α -1,3-galactose, a blood group substance of nonprimate mammals. There is evidence from Australia, Sweden, and the United States that the primary cause of this IgE antibody response is tick bites. These bites characteristically itch for 10 days or more. Diagnosis can be made by the presence of specific IgE to beef, pork, lamb, and milk, and the lack of IgE to chicken, turkey, and fish. Skin prick tests (but not intradermal tests) generally are negative. Management of these cases, now common across the southeastern United States, consists of education combined with avoidance of both ingestion of red meat and further tick bites. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:259-65)

Key words: Anaphylaxis; Delayed reaction to red meat; Galactose- α -1,3-galactose

Anaphylaxis is a well-recognized syndrome that can occur rapidly after exposure to allergens derived from foods, venoms, and medications as well as during allergen immunotherapy. There are several potential features that characterize anaphylaxis, which, in

most cases, make both the diagnosis and the cause obvious. First, the combination of hives (or angioedema), hypotension, and respiratory symptoms is familiar to medical personnel who work in an emergency setting. Second, the onset of symptoms generally occurs within minutes to 2 hours after the exposure, thus limiting the range of events that need to be considered as causal. Third, most of the patients have some history of allergic symptoms or local reactions to the causal agent. Fourth, onset of sensitivity to foods other than fish, shellfish, and tree nuts is considered to be rare after childhood. The present case has many features that do not fit the traditional model but that are representative of a syndrome that is both common in the United States and increasingly recognized in other parts of the world. Before the recognition of the specific IgE antibody involved, the etiology of these cases was not only regarded to be unrelated to food allergy but also was consistently dismissed as being idiopathic or even psychological in nature.

CASE

On June 3, 2012, at 3:00 PM, the patient, 79 years old, collapsed in the lobby of the University of Virginia hospital shortly after she had developed generalized itching and hives. She was found to have a blood pressure of 60/45 mm Hg, and the hospital emergency team treated her with epinephrine, diphenhydramine, intravenous methylprednisolone, and intravenous fluids before transfer to the emergency department and subsequently to the hospital. She had no respiratory symptoms. She recovered steadily over the next few hours but developed an unusual flat, erythematous rash on her arms that was present for 12 hours (Figure 1).

HISTORY

The patient had been working in the hospital for more than 40 years and had a longstanding history of medical issues, including hypertension, for which she was taking low doses of metoprolol and lisinopril. In addition, she reported a history of 2 episodes of hives earlier that summer after eating beef several hours before the episodes and had not been aware of any insect stings on the days of the episodes. After learning of the syndrome of “red meat allergy” from the local papers, she began avoiding ingestion of red meat with the thought that her reactions might be related to this reported allergy. On the day of the reaction, she chose to eat pork for lunch, with the thought that pork was not red meat but rather “the other white meat.” Upon further questioning during follow-up, she reported having had 3 tick bites earlier in the summer that had itched for approximately 10 days.

INVESTIGATION

Results of routine laboratory studies, including metabolic panel and complete blood cell count with differential, were

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Abbreviations used

Alpha-gal- Galactose-alpha-1,3-galactose
LDL- Low density lipoproteins
VLDL- Very low density lipoproteins

unremarkable except for a low eosinophil count. The serum total IgE level was 223 IU/mL, and IgE to galactose alpha-1, 3-galactose (alpha-gal) value was 82.7 IU/mL (Table I). The patient's serum tryptase level 12 hours after the episode was 36.5 ng/mL (reference range, <11.5 ng/mL).

Discharge instructions

The patient was educated in detail about the diagnosis. The management recommended to her at the time of discharge was avoidance of ingestion of mammalian meat and avoidance of environments with a high prevalence of ticks. She was given a prescription for an EpiPen (Dey, Napa, Calif).

DIFFERENTIAL DIAGNOSIS AND POSSIBLE CAUSES

The possible causes of collapse in general are numerous and include common cardiopulmonary, endocrine, and gastrointestinal emergencies. Included in this list is anaphylaxis, which is easily recognized by the combination of generalized pruritus, hives, and hypotension, and which was confirmed in this case with an elevated serum tryptase level.^{1,2} Over the past 20 or more years, we have either seen or helped to investigate patients for whom anaphylaxis was caused by a wide range of events, which, in most cases, was combined with sensitization (Table II). These include venoms, foods, medications, mAbs, and nonsteroidal anti-inflammatory drugs as well as less-common events such as *Trichophyton* sensitization, bites from laboratory rodents, and food-dependent exercise-induced anaphylaxis.³⁻⁶

Over the past 5 years, we have evaluated hundreds of patients with a history of anaphylaxis, angioedema, or generalized urticaria starting 3 to 5 hours after eating "red meat." As in the case of the patient in this case, these patients have serum IgE antibodies to alpha-gal.⁷ This oligosaccharide, a blood group substance of nonprimate mammals, is present on glycolipids and glycoproteins in beef, pork, and lamb, and in the meat and organs of a wide range of mammals.⁸⁻¹⁰ The latter include horse, goat, rabbit, and squirrel as well as mammalian heart, liver, stomach, and kidney. Strikingly, many of the patients correctly identify that their reactions occur after the ingestion of beef or pork but not after ingestion of chicken, turkey, or fish. The cat-pork syndrome can cause confusion because patients with this syndrome, whose primary sensitization is to cat albumin, can become allergic to pork in adulthood due to cross-reactivity between cat albumin and pork albumin.^{11,12} However, the reactions are more rapid, that is, they occur within 1 hour, and generally occur only after ingestion of pork.

HISTORY OF IgE ANTIBODIES TO ALPHA-GAL AND CETUXIMAB-INDUCED HYPERSENSITIVITY REACTIONS

In 1935, Karl Landsteiner identified a blood group "B-like" oligosaccharide on nonprimate red blood cells and reported that all humans had antibodies to this antigen.¹³ Subsequently, it became clear that this antigen, alpha-gal, was a major

transplantation barrier between primates and other mammals.^{9,10}

The fact that mice can make oligosaccharides that are foreign to humans is highly relevant to our story. In 2004, the mAb, cetuximab, was being studied in clinical trials, and it became clear that it was causing hypersensitivity reactions in some southern states. Tina Hatley, MD, in our group carried out preliminary experiments on IgE to this molecule. However, marketing of the mAb was delayed, and it was not until 2006 that the severity of the reactions became obvious.¹⁴ At this time, Hatley, who was working in Bentonville, Arkansas, convinced us to develop a new version of the IgE assay (fluorometric enzyme immunoassay) by using the streptavidin technique, in which streptavidin is coupled to the solid phase of the fluorometric enzyme immunoassay to provide a matrix for the binding of biotinylated novel or purified allergens.¹⁵ We were asked to investigate the reactions to cetuximab, in part because we had already developed the assay for IgE to cetuximab. In collaboration with Christine Chung, MD, from Nashville, Beloo Mirakhur, MD, from Bristol Myers Squibb, and Dan Hicklin, PhD, from ImClone, we demonstrated that the patients who had reactions to cetuximab also had IgE antibodies specific for this molecule before they started treatment.³ We went on to demonstrate that the IgE antibodies were specific for the oligosaccharide on the Fab portion of the mAb. From the known glycosylation of the molecule, we identified alpha-gal as the relevant epitope.¹⁶ Initially, we argued that the glycosylation on the Fc portion of the molecule was not alpha-gal; however, further investigation established that the glycosylation of the Fc portion is "encased" within the 2 halves of the molecule.¹⁷

DELAYED ANAPHYLAXIS TO RED MEAT

Following the discovery that IgE antibodies to alpha-gal were common in our region, we asked whether there were other allergic diseases associated with this antibody. Through testing different groups of patients in our clinics for IgE to alpha-gal, we identified a group of patients who had episodes of generalized urticaria, angioedema, or recurrent anaphylaxis. These patients had no obvious immediate cause for their episodes, but, in several cases, the patients had reported that they thought the reactions might relate to consumption of meat 3 to 5 hours earlier. Skin prick tests with commercial extracts of beef, pork, or lamb produced small wheals (2 to 4 mm in diameter). Wheals of this size, in general, would be interpreted as negative. Intradermal skin tests with commercial meat extracts or skin prick tests with fresh meat extracts demonstrated clearly positive results.⁷ Furthermore, blood tests for specific IgE antibodies to red meats were consistently positive.^{3,7} Over the next 2 years, we rapidly accumulated cases, in large part because of publicity in the press.¹⁸ In fact, it became clear that many patients and 2 allergists had reported delayed anaphylaxis to red meat in previous years. The best description had come to us from Sandra Latimer in Athens, Georgia. In 1989, she described 10 cases of delayed reactions to mammalian meat and made a connection with occurrence of tick bites several weeks or months before the first episode of hives or anaphylaxis. In 1991, her allergist, Antony Deutsch, MD, reported Latimer's findings to the Georgia Allergy Society and to the US Centers for Disease Control and Prevention (CDC). However, no further reports or statements were issued by either of these organizations, possibly because the story seemed so unlikely or because of the lack of a diagnostic blood test at that time.



FIGURE 1. Physical examination of the patient 8 hours after ingestion of pork and 5 hours after anaphylaxis.

TABLE I. Laboratory values of the patient from June 2012 to December 2013

	Jun 2012	Aug 2012	Sep 2012	Dec 2013
Specific IgE (IU/mL; reference range: <0.1 IU/mL)				
Alpha-gal	82.3	47.5	35.7	18.9
Beef	—	4.32	4.80	2.61
Pork	—	2.2	2.20	2.71
Lamb	—	—	—	1.15
Chicken	—	<0.1	—	<0.1
Fish	—	<0.1	—	<0.1
Dust mite	—	<0.1	—	<0.1
Cat	—	0.45	—	0.52
Grass pollen	—	1.10	—	<0.1
Total IgE (IU/mL)	180	111	85.8	50.6
Tryptase (ng/mL)	36.5	—	7.53	—

Although there are several distinctive features of the syndrome, including gastrointestinal symptoms, the most important feature is that patients do not develop any symptoms for at least 2 hours after eating red meat. In most cases, the symptoms are delayed for 3 to 5 hours, but, nonetheless, the symptoms can be severe or even life threatening at that time. Second, all these patients reported meat consumption for many years before the onset of the syndrome, and, indeed, many of the patients were more than 60 years of age. Third, although some patients had a history of allergy, most of the patients had no previous allergic symptoms. Fourth, we have carried out extensive investigation of lung function and asthma symptoms in these patients, and the presence of IgE antibodies to alpha-gal shows no association with asthma.¹⁹ Although most of the cases occur in adults, a very similar syndrome also can occur in children as young as 5 years old.²⁰

THE RELEVANCE OF TICK BITES TO IGE ANTIBODY RESPONSES TO ALPHA-GAL

In 2008, the specificity of the IgE antibodies that caused reactions to cetuximab became known, and it also was clear that reports of delayed reactions to red meat were occurring in the same region as the states in which cetuximab reactions were common. However, it was not clear why these cases were

TABLE II. Causes of anaphylaxis in patients seen by or investigated by us

Immediate responses	
(i) Venom	Honey bee, hornet, yellow jacket, and fire ant
(ii) Foods	Peanut, tree nut, egg, milk, and shellfish; pork (in pork cat syndrome)
(iii) Medications, vaccinations	Penicillins, other antibiotics; cetuximab, infliximab; aspirin, nonsteroidal anti-inflammatory drugs*; Zostavax†
(iv) Bites from laboratory animals	Rat
Delayed or ill-defined time course	
(i) Trichophyton infection and sensitization	
(ii) Thyroid autoantibodies: very high titer*	
(iii) Food-related exercise-induced anaphylaxis	
(iv) Delayed reactions to mammalian meat in patients with IgE to alpha-gal	

*Not related to a specific IgE.

†Related to specific IgE to gelatin, not to alpha-gal (Zostavax; Merck and Co, Inc, Whitehouse Station, NJ).

geographically localized. The first clue came from the simple observation that this region was similar to the region of maximum prevalence of Rocky Mountain spotted fever.²¹ After making this connection, we started to ask questions about tick bites and rapidly became aware that most of the patients with delayed anaphylaxis had experienced bites from adult or larval ticks. The larval ticks, which are approximately 1 mm in diameter, cannot be identified as ticks without a magnifying glass and are commonly referred to as seed ticks or chiggers. The evidence that tick bites caused development of specific IgE to alpha-gal included the following: consistent histories of bites that itched for 2 weeks or more, a significant correlation between IgE antibodies to alpha-gal and IgE to Lone Star tick, and prospective data on the increase in IgE to alpha-gal after known Lone Star tick bites.²¹ In addition, there are accurate CDC maps of the

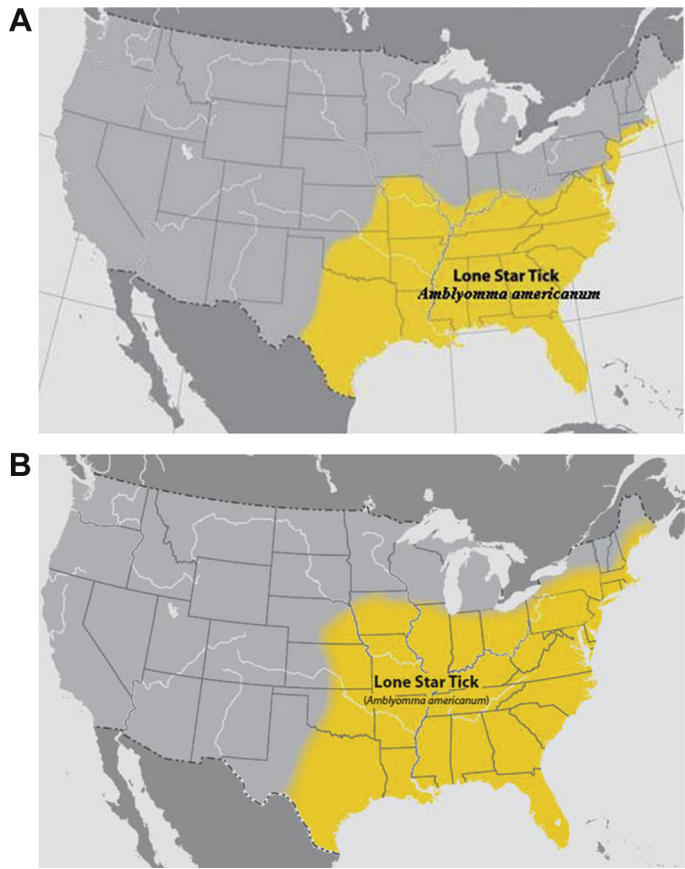


FIGURE 2. Geographic spread of the Lone Star tick, *A americanum*. **A**, 2007, **B**, 2011. (Figures from [CDC.gov](http://www.cdc.gov).)

TABLE III. Worldwide cases of IgE to alpha-gal and delayed anaphylaxis to mammalian meat

Country	Ticks	Food	No. cases	Study, year
Sydney, Australia	<i>I holocyclus</i>	Kangaroo	400	Van Nunen et al, ²² 2009; Mullins et al, ²³ 2012
Nancy, France	<i>I ricinus</i> *	Pork kidney and meat from many species	40+	Morisset et al, ³⁴ 2012
Stockholm, Sweden	<i>I ricinus</i>	Red meat	60+	Hamsten et al, ²⁵ 2013
Japan	—	Beef	30+	Takahashi et al, ³⁷ 2013
Germany	<i>I ricinus</i> *	Pork kidney	50+; 40+	Caponetto et al, ³³ 2013; Jappe, ³⁸ 2012
Virginia, USA	<i>A americanum</i>	Red meat	1800	Commins et al, ⁷ 2009; Commins et al, ²¹ 2011

*Presumed tick species in these areas (not fully investigated).

distribution of the tick *Amblyomma americanum* (Figure 2). In other countries, the ticks that give rise to this response are not the same species (Table III). In Europe, *Ixodes ricinus* was implicated, whereas, in Australia, the relevant tick is *Ixodes holocyclus*.²²⁻²⁵ In contrast, it appears that *Ixodes scapularis*, which is the main vector of Lyme disease in the United States does not induce IgE to alpha-gal. Even more striking is the fact that the bites of *I scapularis* that are associated with transmission of *Borrelia burgdorferi* are not associated with itching.²⁶

MECHANISMS OF ANAPHYLAXIS

Our current understanding of the mechanism of sensitization to the oligosaccharide alpha-gal, a blood group substance of nonprimate mammals, is that it occurs through bites from several different species of ticks. Thus, the patients have IgE antibodies to this hapten, which is present on all mammalian food products.

In some ways this is comparable with sensitization to plant oligosaccharides, such as MUXF3, a hapten on the glycoproteins of many plant species.²⁷⁻²⁹ However, IgE antibodies to such plant-derived cross-reactive carbohydrate determinants are not thought to give rise to symptoms (Figure 3).^{27,30}

The patients with IgE to alpha-gal consistently report that symptoms start 3 to 5 hours after eating meat. Furthermore, in oral food challenge studies done with pork, hives and other symptoms do not develop until at least 2 hours after ingestion.³¹ By contrast, reactions to cetuximab develop rapidly and symptoms often peak within 20 minutes.^{3,14} Similarly, *in vitro* responses of basophils to glycoproteins such as beef thyroglobulin, or cetuximab itself, can be detected within 25 minutes. Skin prick test responses to cetuximab, beef extract, or beef thyroglobulin are all rapid. Thus, there is no reason to think that the delay in response after eating meat reflects a delayed response of

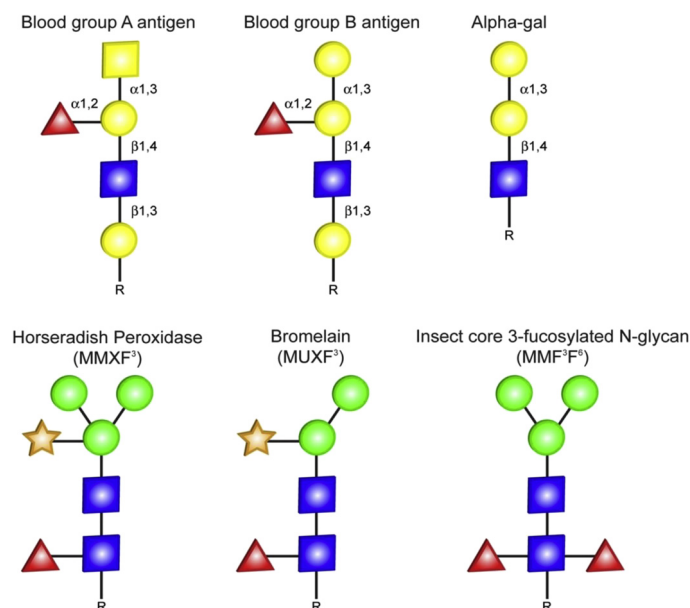


FIGURE 3. Comparison of mammalian blood group–related oligosaccharides (*top*) and plant-derived cross-reactive carbohydrate determinants (CCD) (*bottom*). IgE antibodies to the plant-derived CCDs are not thought to give rise to symptoms. The oligosaccharide structures are shown in the symbolic depiction suggested by the Consortium of Functional Glycomics and are represented as the following: N-acetylglucosamine (blue squares), mannose (green circles), galactose (yellow circles), N-acetylgalactosamine (yellow squares), xylose (orange stars), and fucose (red triangles).³²

basophils or mast cells. The only coherent explanation is that the oligosaccharide is absorbed in some form that enters the circulation slowly. Given that alpha-gal is present on both glycoproteins and glycolipids (including chylomicrons), we think the most likely explanation for the delay in symptoms is a delay in mediator release triggered by low density lipoproteins (LDL) and very low density lipoproteins (VLDL), the metabolic products of chylomicrons that characteristically enter the circulation slowly. Interestingly, during oral food challenge, circulating basophils, assessed *ex vivo*, upregulate the expression of CD63 at the same time that the patients develop symptoms.³¹ However, a proportion of control subjects who were nonallergic also showed delayed in-time upregulation of CD63, although they did not experience any symptoms. At present, we think that the likely explanation for this enigmatic finding is that, although VLDL or LDL can cause basophils to upregulate, the quantity of histamine released is not sufficient to cause symptoms. The implication is that LDL particles with alpha-gal on the surface can cause mast cell mediator release, but this only occurs in individuals with IgE antibodies to alpha-gal. In keeping with this model, 3 of the challenge patients, but none of the control subjects, had tryptase in their circulation after challenge.³¹

CURRENT MANAGEMENT OF DELAYED ANAPHYLAXIS TO RED MEAT

At present, the primary management of this syndrome is to avoid ingestion of red meat, to avoid tick bites, and to educate the patient fully about the management of episodes.

Avoiding “red meat”

Avoidance of “red meat” includes avoidance of ingestion of not only beef, pork, and lamb but also horse, goat, rabbit, and squirrel, among others. It is equally important to note that this

list also includes organs from mammalian sources such as liver, intestine, heart, and kidney. Ingestion of pork kidney, a delicacy in Alsace Lorraine and Germany, has been reported to cause more severe and faster (ie, within 1–2 hours) reactions than ingestion of pork meat.^{33,34} Venison may be included in this list if it has been handled by a butcher; in this case, it may, in addition, contain pork fat (however, if this meat is dressed by a hunter, then it may be low in fat and tolerated without reaction).

In addition to meat, other mammalian products include lard, suet, gelatin, pork rinds, and dairy products. Most patients with IgE to alpha-gal will have positive IgE assays for milk but, nonetheless, will tolerate milk and dairy products. Our current policy is to discuss the relevance of dairy but only to recommend avoidance in cases of patients who continue to have hives or other unexplained symptoms while avoiding ingestion of red meat. Gelatin has been reported to cause severe reactions either in the form of jelly candy and marshmallows or as the intravenous preparations, Haemaccel (Piramal Critical Care Inc, Bethlehem, Pa) and Gelofusine (B. Braun, Melsungen, Germany).^{23,33}

Avoiding tick bites

Most of us who get repeatedly bitten by ticks “ask for it.” In the case of one of the authors of this article (T.P.-M.), major episodes have followed long walks in grassy areas during the summer. Equally, many hikers, hunters, gardeners, and riding enthusiasts spend time in thick vegetation. Although avoidance of tick bites may be possible through use of protective clothing and products such as *N,N*-diethyl-*meta*-toluamide, such protection is often not used because most of the locations in which these bites are occurring are very hot during the summer months. In our area of central Virginia, the larval form of Lone Star ticks are the most aggressive and are particularly prevalent in August and early September. Individuals who live in urban settings

where ticks are usually less prevalent and those who only hike on well-used trails or fire trails may be able to avoid ticks completely. We have certainly noted a decrease in the level of IgE to alpha-gal in such individuals, which may, in turn, make them much less prone to symptomatic attacks.

Management of episodes

The management of anaphylaxis at all ages includes antihistamines, epinephrine, steroids, and intravenous fluids. However, in older adults, particularly those with cardiac risk factors or a history of cardiac disease, we tend to recommend less aggressive use of epinephrine due to risk of precipitating a cardiac event. In fact, one of our colleagues in Lynchburg, Virginia reported that 2 adult patients were referred to him by a cardiologist because they had experienced a heart attack shortly after being given epinephrine. Many of the patients with this syndrome were already more than 60 years of age when they first presented with symptoms. Thus, older patients should be instructed to be careful about exposure, to take Benadryl orally or even intramuscularly, to make sure that someone who is able to administer epinephrine is aware of the symptoms suggestive of a reaction, and to only use epinephrine if the attack progresses beyond hives. The question of when to give epinephrine is primarily one to be decided upon by the patient and first responders, rather than emergency department providers. Most patients who arrive in the emergency department do not receive epinephrine because their condition is already improving by the time they arrive in this setting.

DISCUSSION

The syndrome of delayed anaphylaxis to red meat was initially recognized by patients, but, for many reasons, was not taken seriously by physicians, including allergist/immunologists. The lack of enthusiasm for this syndrome could be easily understood because its features run counter to many established teachings about food allergy and anaphylaxis. These established teachings include the following: new onset of allergic reactions to meat is rare in adults; intradermal skin tests are not useful in evaluating food allergy; severe, immediate hypersensitivity reactions to food start within minutes to 2 hours after exposure; and sensitization to food occurs through oral exposure.

There still are many aspects of the syndrome that are not well understood.

1. It is not clear why the tick bites induce such high levels of IgE antibody and why the response is specific for this oligosaccharide. It is clear that the tick carries alpha-gal, both from inhibition studies with the extract²¹ and from staining sections of the tick.²⁴ However, this is not the only oligosaccharide present on this tick. Currently, we are considering the possibility that the IgE antibody response to alpha-gal involves direct switch outside a germinal center and that the response involves very little somatic hypermutation.^{35,36}
2. The basis for the delay in symptoms is not clear. Our hypothesis is that the timing of the reactions reflects the time at which alpha-gal appears in the circulation displayed as repeating epitopes on a particle such as LDL. We also are well aware that some subjects who have IgE to alpha-gal do not experience symptoms. Whether this reflects a difference in carbohydrate absorption or a relative resistance to mast cell mediator release is not clear.

3. Although most allergists in the southeastern United States believe that the prevalence of this syndrome has increased, it is difficult to prove that a newly described syndrome was less common previously. In theory, the increase could be due to a change in the tick population, such as the presence of a different species of *Rickettsia*, the spread of a species of tick that was previously not present, or a simple increase in the population of the Lone Star tick. However, the evidence favors a combination of the increasing geographic range of this tick and the massive increase in number of ticks secondary to the increase in the deer population over the past 60 years (before 1950, deer were few in number due to virtual "extirpation" in the Piedmont region of Virginia and in the Carolinas). It seems unlikely that we will be able to control the tick population, and, in turn, tick bites, unless the deer population also is controlled.

Management of this syndrome consists primarily of education combined with specific advice about avoiding ticks and avoiding ingestion of mammalian-derived products. Currently, there are no interventional studies designed to control sensitization or control the reactions. At present, the geographic range of this tick seems to be steadily expanding, and it is likely that the number of cases will continue to increase.

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